The amendments to the claims are to cancel claims 2, 3 and 10 without prejudice and to amend claim 1 to include to subject matter thereof. Also, claims 12 and 13 were amended, along with claim 1, to delete the terminology "without the need to recur to hypotheses".

The objected to term "condition" was defined as "pathogenic or any other condition", as suggested by page 5 of the present Specification.

The objected to term "reference" has now been defined in the claims as supported on page 3 in lines 1 to 3 of the present Specification as follows: "The distribution of low-molecular weight peptides in a representative cross-section of defined controls is used as a reference." The added language in claim 1 "to produce a differential peptide display" is found on page 5 in lines 16 to 17 of the present Specification.

In claim 1, the term "organism" has been defined based upon claim 10. In claim 13, the objected-to term "causally" has now been canceled.

On page 4 of the Office Action was an objection to the claims as being incomplete. In response to this objection, a sample of the organism is contacted; and the low-molecular weight peptides

are being detected; and a pathogenic or other condition is correlated. These low-molecular weight peptides have a molecular weight of not more than 30,000 Dalton, (original claim 3), now recited in claim 1.

In the Office Action, the Examiner objected to the terms "conditions", "hypotheses" and "reference". These terms have been explained above.

In regard to claim 4, this claim is meant to define a lower limit for the mentioned "low-molecular weight peptides", i.e. the smallest molecules to be measured are dipeptides, consisting of two amino acids.

In regard to claim 8, this claim is meant to further define the method of the invention. Peptides can be characterized by several features, i.e. iso-electric point, sequence or molecular weight.

In regard to Claim 11, the steps necessary to obtain samples from the cited organisms are known in the art. All known methods are acceptable as long as the samples contain low-molecular weight peptides. The objection to "and/or" was overcome by amending the last part of the claim to recite a Markush group.

The Patent Examiner further objected to the term "organism". The term is meant to cover all kind of "peptide containing beings", i.e. man, animals, plants, parasites, bacteria and the like. The measurement starts from a sample of these targets. In case of the human being or animal a sample may be taken from blood or urine. In case of a plant it may be a leave. In case of very small organisms, such as bacteria or cells of a cell culture it may be more appropriate to take the whole cell or even several of them from one cell culture bottle or the like. As mentioned above, claim 1 recites the language of claim 10 as a Markush group.

The Patent Examiner also objected to the phrase "without the need to recur to hypothesis". This language means that it is not necessary to know the sequence of function, the weight or the like of the peptide to be measured. From a sample something like a peptide profile is established which can be compared to profiles from other samples. Conclusions are drawn from the comparison of two or more profiles. This objected-to terminology has been canceled.

For all these reasons, all the claims are in complete compliance with the requirements of 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

The Applicants comment upon the prior art rejections of the

claims as follows.

The present invention is directed to a diagnostic method. It provides a general method for identifying the condition (e.g. healthy or suffering from one or more diseases) of an organism. The method employs references not only to healthy organisms, but also includes several references from organisms suffering from different diseases. Having compiled sufficient references, the measurement of peptides from a further organism in question provides information about the condition or status of the organism by comparison to these previously compiled references. It is part of the inventive method to collect these necessary references.

As an example, if reference measurements have revealed that a foreign disease X is affecting an organism, then disease X typically causes the concentration of peptide A and B to increase, while peptide C is lowered, and that a new peptide D will appear in comparison to healthy organisms. Then one would logically assume that a further organism showing also increases in peptides A and B, plus a lowering of peptide C, and having a new peptide D would also suffer from illness X. For the method of the present invention it is not necessary to know the sequence or the physiological role of peptides A, B, C, and D. This is what is meant by the terminology "without the need to recur to hypotheses". It is not necessary to create a hypotheses about the function or source of peptide D. This

is in contrast to conventional methods wherein e.g. an infection with Hepatitis is identified by the analysis of the Hepatitis antigen or the analysis of proteins of the clotting cascade to identify the nature of a clotting disease.

The Patent Examiner has cited *Ausubel*, "Short Protocols in Molecular Biology". The Office Action is correct that *Ausubel* discloses a number of methods for protein analysis. Although the claimed method of the present invention uses methods for the analysis of peptides it does not read on methods disclosed in *Ausubel*. For example, *Ausubel* discloses immunoaffinity chromatography. Immunoaffinity chromatography requires the use of antibodies bound to a matrix e.g. sepharose. Because the antibodies in the prior art are directed against a peptide or a protein, immunoaffinity chromatography can only purify special peptides for which antibodies are available. This requires high-molecular weight peptides and not the claimed low-molecular weight peptides of not more than 30,000 Daltons, recited by claim 1.

Furthermore, *Ausubel* discloses metal-chelate affinity chromatography. Metalchelate affinity chromatography requires the presence of a so-called His-Tag at the protein. Thus only special proteins can be analyzed through this method.

Ausubel further discloses reversed-phase HPLC, ion-exchange

HPLC and size-exclusion HPLC. These methods differ from the claimed method of the present invention in that they are not used to detect the condition of an organism by relating the low-molecular weight peptides to references from other organisms. Furthermore, size-exclusion and ion-exchange HPLC do not permit any detection or characterization of low molecular weight peptides, as claimed.

Harry et al disclose methods for the antigen detection of HIV. These antigens mainly are derived from the major HIV core protein p24, (See page 242, left column). Therefore, all assays are directed from the detection of this protein or fragments thereof. These methods are based on the hypotheses that the detected protein or fragment is relevant for the condition of an organism, e.g. whether or not the organism is infected with HIV. As it is explained above, the method of the present invention in contrast relies on the analysis of low molecular weight peptides without knowing their actual function.

Additionally, *Harry et al* relies on indirect assay methods, see for example page 241, right column, whereas the present invention is directed to direct measurement methods. Also, *Harry* fails to teach the claimed low molecular weight peptide detection and characterization, wherein the molecular weight is not more than 30,000 Dalton as claimed in claim 1.

Jimenez et al discloses the measurement of neuropeptide expression and processing in the neurons of the mollusc *Lymnaea stagnalis.* Most of neuropeptides were known as can be derived from the introduction and especially figure 1, see further first two sentences of "Results and Discussion" on page 405. This is in contrast to the method of the present invention which detects low-molecular weight peptides of not more than 30,000 Dalton. It is not necessary to know weight, concentration, or function of the peptides. Furthermore, *Jimenez et al* have not related the measurements to a reference from an organism or to references from different organisms in different conditions. *Jimenez* do not provide any conclusions about the condition of an organism.

Jiminez on page 404 in the right hand column discloses that matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS), pioneered by *Karas et al (1987)* and recently shown to be useful in the analysis of biological tissue (*van Veelan et al., 1993)*, can be used for direct mass analysis of intact peptides in single neurons. MALDI-MS can detect high-molecular-weight substances, is extremely sensitive, and can tolerate more impurities in the sample than other mass spectrometric methods.

Thus, *Jimenez* can only detect high-molecular weight substances, and does not detect the claimed low molecular weight peptides, which have a molecular weight of not more than 30,000

Dalton, as recited by claim 1.

Finally, none of the prior art references discloses the detection of qualitative and quantitative changes. This is an important improvement and advantage of the present invention, as discussed in the paragraph bridging pages 7 and 8 of the present Specification, as follows.

The data about patients with a known basic disease obtained from the above mentioned steps are compared to the similarly obtained data from a healthy reference population. Both qualitative changes (e.g., the occurrence of new peptides or the lacking of peptides) and quantitative changes (the increased or decreased occurrence of individual peptides) are detected. If required, the targets defined by the comparative analysis may further be purified and identified by methods of peptide chemistry known to those skilled in the art. The sequence information obtained can then be compared with protein and nucleic acid data bases and subsequently with data from the literature. The relevance of the represented peptides with respect to the examined disease is checked by functional studies and by screening with appropriate groups of patients.

For all of the above reasons, none of the prior art references provides an identical disclosure of the claimed invention. Hence,

the present invention is not anticipated under 35 U.S.C. 102. Withdrawal of this ground of rejection is respectfully requested.

Also, none of the prior art references teaches or suggests the present invention as claimed and none of the prior art references provides a basis for any rejection of the claims under 35 U.S.C. 103. A prompt notification of allowability is respectfully requested.

Respectfully submitted,

WOLF-GEORG FORSSMANN ET AL PCT

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Encl.: Copy of Petition for Two Month Extension of Time for a Small Entity

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on February 8, 2001.

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Lisa L. Vulpis